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Authors
Seldin, Marcus M
Wong, G William

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Regulation of tissue crosstalk by skeletal muscle-derived myonectin and other myokines

Marcus M. Seldin and G. William Wong*

Department of Physiology and Center for Metabolism and Obesity Research; The Johns Hopkins University School of Medicine; Baltimore, MD USA

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Abbreviations: CTRP, C1q/TNF-related protein; FATP, fatty acid transporter; FABP, fatty acid binding protein; UCP1, uncoupling protein-1; FGF-21, fibroblast growth factor-21; Insl6, insulin-like 6; Fstl-1, follistatin-like 1; LIF, leukemia inhibitory factor; IL, interleukin

The integrated control of animal physiology requires intimate tissue crosstalk, a vital task mediated by circulating humoral factors. As one type of these factors, adipose tissue-derived adipokines have recently garnered attention as important regulators of systemic insulin sensitivity and metabolic homeostasis. However, the realization that skeletal muscle also secretes a variety of biologically and metabolically active polypeptide factors (collectively called myokines) has provided a new conceptual framework to understand the critical role skeletal muscle plays in coordinating whole-body energy balance. Here, we highlight recent progress made in the myokine field and discuss possible roles of myonectin, which we have recently identified as a potential postprandial signal derived from skeletal muscle to integrate metabolic processes in other tissues, such as adipose and liver; one of its roles is to promote fatty acid uptake into cells. Myonectin is also likely an important mediator in inter-tissue crosstalk.

Skeletal muscle, the largest organ in the human body, plays a vital role in maintaining whole-body metabolic homeostasis. In particular, in response to insulin this organ takes up a major proportion of the circulating postprandial glucose via GLUT4-mediated transport, then metabolizes or stores it in the form of glycogen.[1] Impaired insulin responsiveness in muscle is a hallmark of type 2 diabetes.[2] The recent discovery that skeletal muscle secretes a variety of myokines which can act in an autocrine, a paracrine and/or an endocrine fashion to regulate metabolic and inflammatory processes, gives a new dimension to the role of muscle in coordinating integrated physiology.[3] Further, proteomics approaches to cataloging the secretome of cultured mouse and human myotubes have revealed hundreds of secreted proteins,[4,5] many of which likely play roles in diverse cellular processes. The inter-tissue crosstalk mediated by myokines undoubtedly provides a greater sense of appreciation for the complexity of metabolic circuits governing systemic energy balance.

*Correspondence to: G. William Wong; Email: gwwong@jhmi.edu
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Myostatin, the first described myokine, is a secreted protein belonging to the TGF-β superfamily and a negative regulator of muscle growth.[6] A loss-of-function mutation in myostatin in human or absence of myostatin in knockout mice results in a striking doubling of muscle mass.[6,7] Since the discovery of myostatin, the functions of other myokines such as IL-6,[3] FGF-21,[8,9] insulin-like 6 (Insl6),[10] follistatin-like 1 (Fstl-1; also known as TSC-36),[11] LIF,[12] IL-7,[13] IL-15,[14] musclin[15] and irisin[16] have been described. These myokines either act locally within skeletal muscle, serving as autocrine/paracrine factors, or circulate in blood as endocrine factors linking skeletal muscle to regulation of physiological processes in other tissues. In the context of metabolism, IL-6 is the most extensively characterized myokine.[3,17,18] Secreted by skeletal muscle fiber in response to exercise, IL-6 improves whole-body insulin sensitivity and dampens inflammation, providing a link between exercise and improvement in systemic metabolic parameters.[17-19] However, the contrasting role of IL-6 as a pro-inflammatory cytokine that induces hepatic insulin resistance has yet to be fully reconciled.[20,21] In mice, Fstl-1 links skeletal muscle to the vasculature, promoting endothelial cell function and revascularization in ischemic tissue.[11] A gain-of-function mouse model demonstrates a role for muscle-derived IL-15 in regulating fat mass in response to metabolic insults resulting from high fat-feeding,[14] highlighting a muscle-adipose axis, which controls systemic energy balance.

Much excitement and discussion have surrounded the identification of Fndc5/Irisin, a gene whose expression is regulated by the transcriptional co-activator, PGC1-α.[16] Indeed, it was discovered as a gene upregulated in skeletal muscle of mice overexpressing a PGC1-α transgene. Fndc5 is synthesized as a type I transmembrane protein; proteolytic processing generates a soluble form (designated as irisin) that circulates in blood. Exercise increases circulating levels of irisin in humans and mice. Remarkably, adenovirus-mediated overexpression of irisin turns on the thermogenic program in subcutaneous fat depots by inducing the "browning" of white adipose tissue. However, only a subset of cells within the white adipose tissue acquires brown adipocyte-like phenotype; thus, the extent of "browning" of white adipose tissue

may be variable. An increased number of uncoupling protein-1 (UCP-1)-expressing brown adipocyte-like cells within the white adipose tissue enhances fat oxidation, resulting in enhanced energy expenditure and improved systemic insulin sensitivity. Thus, the metabolic action of muscle-derived irisin on fat depots provides one molecular mechanism accounting for the benefit of exercise. However, despite a major resurgence in the study of brown fat,[22] the purported role of this tissue in maintaining energy balance by burning off excess calories remains a hotly debated issue.[23]

Unlike other myokines, whose expression is not restricted to skeletal muscle, myonectin is a novel myokine expressed predominantly by the skeletal muscle.[24] We identified myonectin/CTRP15 as a novel secreted protein possessing a globular C1q domain, the signature feature shared by other recently-characterized C1q/TNF-related proteins (CTRP1–14),[25-28] several of which are fat tissue-derived adipokines with important metabolic functions.[29-31] The term "myonectin" was inadvertently used to re-designate CTRP5 in a recent study.[32] To prevent confusion in nomenclature, CTRP5 retains its original designation[25,33,34] and CTRP15 be referred to as myonectin. Of the CTRPs, myonectin is the only one whose expression is restricted to skeletal muscle. Interestingly, oxidative, slow-twitch muscle fibers (e.g., soleus) tend to express a higher transcript level of myonectin relative to glycolytic, fast-twitch fiber types (e.g., plantaris).

Expression and circulating levels of myonectin are subjected to metabolic control. Overnight fasting substantially reduces, while re-feeding dramatically increases, its mRNA and serum levels. Intriguingly, circulating levels of myonectin are increased to the same extent when overnight-fasted mice are gavaged with a bolus of glucose or emulsified lipid, suggesting that myonectin expression and secretion is highly responsive to an acute alteration in the metabolic state of skeletal muscle after nutrient intake. Similar transcriptional upregulation of myonectin expression can be recapitulated in cultured mouse myotubes upon the addition of glucose or free fatty acids (e.g., palmitate), suggesting that myonectin may be a nutrient-responsive myokine secreted in response to nutrient flux through skeletal muscle.

Exercise is known to have profound beneficial effects on improving systemic insulin sensitivity and other metabolic parameters, but the underlying molecular mechanism remains incompletely understood.[35] Interestingly, mice given access to a running wheel for two weeks display elevated myonectin expression in skeletal muscle and in circulation compared with mice with access to a locked wheel. However, it remains to be determined whether an acute bout of exercise is directly coupled to increased expression of myonectin, or upregulated expression of myonectin mRNA and protein is secondary to increased meal consumption following each bout of voluntary exercise,[36] thus mimicking the "re-feeding" state known to induce myonectin expression and secretion.

Additionally, administration of recombinant myonectin to mice reduces circulating free fatty acid levels without affecting adipose tissue lipolysis.[24] It appears that myonectin does so by promoting free fatty acid uptake into cells. In cultured adipocytes and hepatocytes, recombinant myonectin enhances fatty acid uptake through transcriptional upregulation of genes (e.g., *CD36*, *FATP1*, *Fabp1* and *Fabp4*) known to be involved in fatty acid uptake, an effect comparable to that in cells constitutively overexpressing those proteins (e.g., CD36, FATP1, FATP4).[37] Given that its expression and circulating levels are acutely elevated by feeding, we propose that myonectin functions as a novel postprandial signal derived from skeletal muscle to integrate metabolic processes in other tissues, such as adipose and liver, and one of those functions is to promote free fatty acid uptake into cells (**Fig. 1**). Future studies using gain- and loss-of-function mouse models will further clarify the function and mechanism of action of myonectin in normal physiology and in disease states.

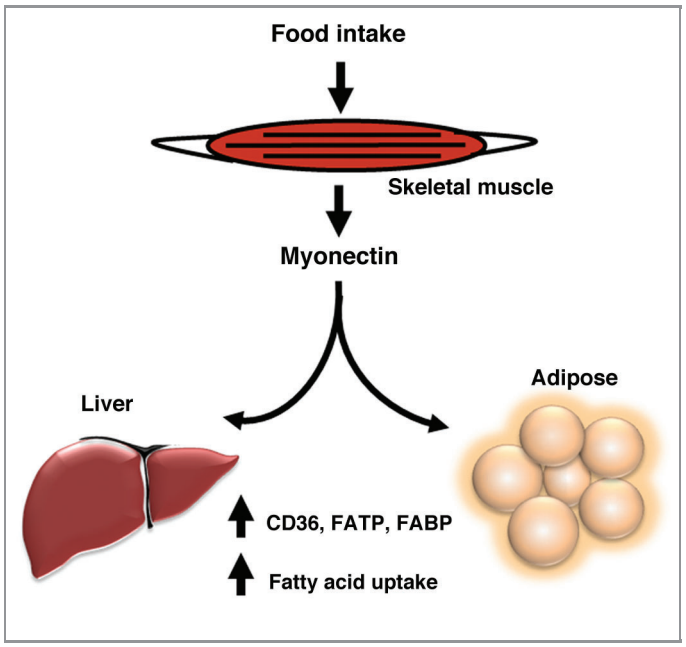

Figure 1. A proposed model of myonectin function. Nutrient intake by skeletal muscle upregulates the expression and secretion of myonectin, resulting in an increased circulating level of the protein. Myonectin induces the expression of CD36, fatty acid transport proteins (FATP), and fatty acid binding proteins (FABP) in hepatocytes and adipocytes, resulting in enhanced fatty acid uptake into hepatocytes and adipocytes.

Analogous to the importance of fat tissue-derived adipokines in regulating systemic insulin sensitivity and glucose and lipid metabolism in multiple tissue compartments,[38] skeletal muscle-derived myokines are poised to play an equally important role in mediating inter-tissue crosstalk to control integrated physiology. In a broader context, elucidating the myokine-regulated metabolic circuits will provide valuable insights into complex networks governing energy homeostasis, the disruption of which likely contributes to metabolic diseases.

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